International Pharmaceutical Excipients Council
Of The Americas

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Marshall Steinberg, Ph.D.
Chairman

August 27, 1999

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane, RM 1061
Rockville, MD 20852

Guidance Docket # 99D-0529

Re: Guidance for Industry, Changes to an Approved NDA or ANDA

Gentlemen:

IPEC Americas represents many of the major makers and users of pharmaceutical excipients in the United States. These materials are used in essentially all approved drugs and are critical to the performance of the dosage forms. Most of these materials are manufactured to comply with compendial standards such as the United States Pharmacopeia/National Formulary (USP/NF) and are used for multiple applications. Excipients are different than bulk active drug substances in that individual excipients are used in a broad spectrum of drug applications and dosage forms to provide varying types of functionality.

Several areas in the proposed guidance document affect and are of concern to IPEC-Americas member companies, for example:

- The guidance appears to produce an additional regulatory burden rather than less to pharmaceutical and excipient manufacturers. This appears to conflict with the intention of Congress when it passed the FDAMA legislation.

- Due to the expiration of 21 CFR 314.70 on November 21, 1999, confusion within the industry may exist as to how best to coordinate manufacturing changes until such time as the new regulation is issued. FDA has stated that the revised regulation will not be published by November 21st and that a re-issued guidance document will be used to assist companies in making decisions about changes until such time as new regulations are implemented. However, we understand that a new guidance document will not be available for industry analysis until shortly before 21 CFR 314.70 expires. This does not appear to allow sufficient time to adequately prepare for and train employees to follow new internal company procedures, should the proposed additional changes be required.

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- More importantly, language in the proposed guidance indicates that future changes to required compendial standards, which previously have been considered as changes that could be reported to FDA in an Annual Report, now appear to require submission of an NDA or ANDA supplement. This change could have significant negative impact to both the industry and FDA. It also is likely to slow progress of both International Harmonization and the compendial revision process, as well as significantly increase costs to both FDA and the affected industry.

IPEC-Americas representatives attended the FDA meeting held on August 19, 1999 and paid close attention to the statements of Mr. Joseph G. Valentino of the United States Pharmacopeial Convention. We agree that if changes to a compendial standard potentially will require the submission of a supplement to the agency, the amount of non-value added paperwork which necessarily will be generated, will be significant. We submit that the result will be a large burden on industry and FDA without any apparent improvement in the safety or efficacy of products involved.

IPEC Americas agrees with views expressed by the trade organizations present on April 19 with respect to the reporting of changes in compendial standards, and recommends that such changes continue to be reported in a company's annual report.

We respectfully suggest that FDA may want to consider the impact that the proposed approach is likely to have on pharmaceutical users of excipients when a compendial change is made in an excipient monograph. Your attention is invited to the following examples:

Hydroxypropyl Methylcellulose – Impact of International Harmonization

As the agency is aware, an existing USP/NF monograph for Hydroxypropyl Methylcellulose (HPMC) is in the process of being harmonized with European Pharmacopeia (PhEur) and Japanese Pharmacopeia (JP) requirements. The harmonization process will require changes in test methods and certain parameter limits. These changes have been proposed to provide uniform requirements within the various regions on the material which is used in numerous global drug applications. According to FDA's Inactive Ingredient Guide, at least **659** NDAs have been approved containing HPMC. In addition, there are other NDAs which contain HPMC as part of a multi-component mixture. These are listed in the Inactive Ingredient Guide by cross-reference to a formulation number. We are advised there are over **361** references to various Opadry formulations containing HPMC which are used in film coating; there are probably others as well.

Thus, pursuant to the proposed guidance and regulation and following adoption of a harmonized monograph for HPMC, over **1020** Supplements potentially would have to be filed

with FDA and approved before the pharmaceutical companies could utilize HPMC in their products so as to avoid being defined as adulterated for not meeting USP/NF requirements. We wonder how FDA will be able to process this many supplements? We also ask the agency to consider the impact a flood of supplement applications could have on the nation's supply of certain critical drugs that contain HPMC.

Lactose – The Possible Impact of a Simple Deletion of a Test

In the Eighth Supplement to USP23/NF18 (Official May 15, 1998), USP deleted a requirement for testing for Organic Volatile Impurities (OVIs) in the monographs for Lactose (anhydrous and monohydrate). As there are no organic solvents used in the manufacture of these materials, it was deemed unrealistic to expect that any OVIs would be present. It was felt that requiring an OVI test to be run on Lactose was of no value and was superfluous. As the Agency recalls, this type of change is routinely made to excipient monographs to improve them and make them more consistent with current scientific thinking. However, it would be difficult to describe this type of change as one which "***provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess***". As a result, a reasonable interpretation of the proposed guidance could lead one to conclude that approval of a supplement would be required before lactose, prepared in the new manner, could be used in an approved drug. As Lactose is listed in the FDA's Inactive Ingredient Guide as being present in approximately **2038** approved NDAs, the above change could require over **2038** supplements being filed for lactose-containing products. If our understanding is correct, we fail to see the rationale for such a requirement.

We appreciate the opportunity to submit comments on the proposed guidance document and hope the agency will find them useful.

Sincerely,

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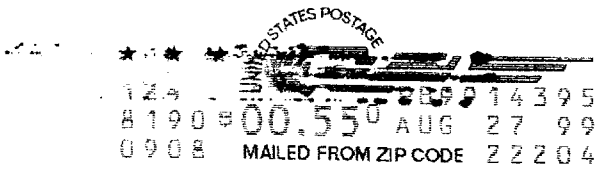

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